Exhibit F

Centers for Disease Control and Prevention

COVID-19

Science Brief: COVID-19 Vaccines and Vaccination

Updated Sept. 15, 2021 Print

Summary of Recent Changes

Last updated September 15, 2021

- Data were added indicating that COVID-19 vaccination remains highly effective against COVID-19 hospitalization and death caused by the Delta variant of SARS-CoV-2.
- Data were added from studies published since the last update that further characterize reduced COVID-19 vaccine effectiveness against asymptomatic and mild symptomatic infections with the Delta variant of SARS-CoV-2.
- Data were added from studies published since the last update that suggest decreased vaccine effectiveness against SARS-CoV-2 infection, symptomatic disease, and hospitalization in several groups of immunocompromised persons and potential benefit of a third dose of COVID-19 vaccine in immunocompromised populations.
- Data were added summarizing several small studies of heterologous COVID-19 vaccination series (i.e., mixed schedules), which found that a dose of adenovirus vector vaccine followed by a dose of mRNA vaccine elicits antibody responses at least as high as two doses of mRNA vaccine.
- Data were added from recent studies examining the duration of protection conferred by COVID-19 vaccination.
- Data were added from recent studies describing clinical outcomes and transmissibility of SARS-CoV-2 infections in fully vaccinated persons.

View Previous Updates

Key Points

- All COVID-19 vaccines currently approved or authorized in the United States (Pfizer-BioNTech/Comirnaty, Moderna, and Janssen [Johnson & Johnson]) are effective against COVID-19, including against severe disease, hospitalization, and death.
- Available evidence suggests the currently approved or authorized COVID-19 vaccines are highly effective against hospitalization and death for a variety of strains, including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2); data suggest lower effectiveness against confirmed infection and symptomatic disease caused by the Beta, Gamma, and Delta variants compared with the ancestral strain and Alpha variant. Ongoing monitoring of vaccine effectiveness against variants is needed.
- Limited available data suggest lower vaccine effectiveness against COVID-19 illness and hospitalization among immunocompromised people. In addition, numerous studies have shown reduced immunologic response to COVID-19 vaccination among people with various immunocompromising conditions.
- The risk for SARS-CoV-2 infection in fully vaccinated people cannot be completely eliminated as long as there is continued community transmission of the virus. Early data suggest infections in fully vaccinated persons are more commonly observed with the Delta variant than with other SARS-CoV-2 variants. However, data show fully vaccinated

commonly observed with the Delta variant than with other SARS-CoV-2 variants. However, data show fully vaccinated persons are less likely than unvaccinated persons to acquire SARS-CoV-2, and infections with the Delta variant in fully vaccinated persons are associated with less severe clinical outcomes. Infections with the Delta variant in vaccinated persons potentially have reduced transmissibility than infections in unvaccinated persons, although additional studies are needed.

- This updated science brief synthesizes the scientific evidence supporting CDC's guidance for fully vaccinated people and will continue to be updated as more information becomes available.

Background

COVID-19 vaccination is a critical prevention measure to help end the COVID-19 pandemic. COVID-19 vaccines are now widely available in the United States, and CDC recommends all people 12 years and older be vaccinated against COVID-19.

On August 23, 2021, the U.S. Food and Drug Administration (FDA) approved an mRNA vaccine (Pfizer-BioNTech/Comirnaty) as a 2-dose series for prevention of symptomatic COVID-19 in persons aged ≥16 years. This vaccine is also authorized under an Emergency Use Authorization (EUA) to be administered to prevent COVID-19 in persons aged 12-15 years. A second mRNA vaccine (Moderna), as well as a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector vaccine (Janssen vaccine [Johnson & Johnson]) are authorized under an EUA for use in persons aged ≥18 years. Both mRNA vaccines are also authorized for administration of an additional dose to certain immunocompromised persons.

People are considered fully vaccinated if they are ≥2 weeks following receipt of the second dose in a 2-dose series (mRNA vaccines), or ≥2 weeks following receipt of a single-dose vaccine (Janssen vaccine).*

Public health recommendations for people fully vaccinated with FDA-approved or FDA-authorized COVID-19 vaccines consider evidence of vaccine effectiveness against symptomatic COVID-19 with and without severe outcomes, as well as vaccine impact on SARS-CoV-2 transmission. Other individual and societal factors are also important when evaluating the benefits and potential harms of additional prevention measures (e.g., masking, physical distancing) among vaccinated individuals. The Advisory Committee on Immunization Practices and CDC routinely consider individual health benefits and risks along with factors such as population values, acceptability, and feasibility of implementation when making vaccine recommendations.(1) These factors were also considered when developing CDC's interim public health recommendations for fully vaccinated people.

In this scientific brief, we summarize evidence available through August 24, 2021, for the currently approved or authorized COVID-19 vaccines (administered according to the recommended schedules) and additional considerations used to inform public health recommendations for fully vaccinated people, including:

- Vaccine efficacy and effectiveness against SARS-CoV-2 infection in the general population as well as among immunocompromised persons
- Vaccine effectiveness of heterologous (mixed) vaccination series
- Vaccine performance (i.e., immunogenicity and effectiveness) against emerging SARS-CoV-2 variant viruses, with a particular focus on the Delta (B.1.617.2) variant

Current evidence indicates that fully vaccinated people without immunocompromising conditions are able to engage in most activities with low risk of acquiring or transmitting SARS-CoV-2, with additional prevention measures (e.g. masking) where transmission is substantial or high.

Emerging SARS-CoV-2 viral variants

As of August 28, 2021, the Delta variant of concern (B.1.617.2) is the predominant variant in the United States, with 99% of sequenced specimens being identified as Delta; current data on variant prevalence can be found on CDC's website. The Delta variant, first detected in India, has been shown to have increased transmissibility, potential reduction in neutralization by some monoclonal antibody treatments, and reduction in neutralization by post-vaccination sera.(2)

Other variants that are either no longer detected or are circulating at very low levels in the United States include: Alpha (B.1.1.7), first detected in the United Kingdom; Beta (B.1.351), first detected in South Africa; Gamma (P.1), first detected in Japan/Brazil; Iota (B.1.526), first detected in the United States-New York; Eta (B.1.525), first detected in the United

Kingdom/Nigeria; Kappa (B.1.617.1) and B.1.617.3, first detected in India. These variants have mutations that alter the receptor binding domain of the spike protein and have variable impact on vaccine effectiveness (notably the E484K/Q mutation in Beta, Gamma, Eta, Iota, Kappa, and B.1.617.3; the N501Y mutation occurring in Alpha, Beta, and Gamma; the E417T/N mutations in Beta and Gamma; and the L452R mutation in Delta, Kappa and B.1.617.3).(2) Vaccine performance against emerging SARS-CoV-2 variants is an important consideration when evaluating the need for prevention measures in vaccinated people and will require continued monitoring.

COVID-19 vaccine efficacy, effectiveness, and immunogenicity

Immunogenicity is the generation of effective protective immunity against a vaccine antigen as measured by laboratory tests. Vaccine efficacy refers to how well a vaccine performs in a carefully controlled clinical trial, and effectiveness describes its performance in real-world observational studies. Evidence demonstrates that the approved or authorized COVID-19 vaccines are both efficacious and effective against symptomatic, laboratory-confirmed COVID-19, including severe forms of the disease. In addition, as shown below, a growing body of evidence suggests that COVID-19 vaccines also reduce asymptomatic infection and transmission. Substantial reductions in SARS-CoV-2 infections (both symptomatic and asymptomatic) will reduce overall levels of disease, and therefore, SARS-CoV-2 virus transmission in the United States. Investigations are ongoing to further assess the risk of transmission from fully vaccinated persons with SARS-CoV-2 infections to other vaccinated and unvaccinated people. Early evidence suggests infections in fully vaccinated persons caused by the Delta variant of SARS-CoV-2 may be transmissible to others; however, SARS-CoV-2 transmission between unvaccinated persons is the primary cause of continued spread.

Animal challenge studies

Rhesus macaque challenge studies provided the first evidence of the potential protective effects of Pfizer-BioNTech, Moderna, and Janssen COVID-19 vaccines against SARS-CoV-2 infection, including both symptomatic and asymptomatic infection. Vaccinated macaques developed neutralizing antibodies that exceeded those in human convalescent sera and showed no or minimal signs of clinical disease after SARS-CoV-2 challenge.(3-5) In addition, COVID-19 vaccination prevented or limited viral replication in the upper and lower respiratory tracts, which may have implications for transmission of the virus among humans.(3-5)

Vaccine efficacy from human clinical trials

Clinical trials subsequently demonstrated the FDA-approved or authorized COVID-19 vaccines to be efficacious against laboratory-confirmed, symptomatic COVID-19 in adults, including severe forms of the disease, with evidence for protection against both symptomatic and asymptomatic SARS-CoV-2 infection (6-12) (**Box**). Trial data demonstrated 100% efficacy of the Pfizer-BioNTech vaccine against laboratory-confirmed, symptomatic COVID-19 in adolescents 12–15 years old; this estimate was based on small numbers of cases and prior to emergence of the Delta variant.(13)

Clinical trial data suggest that the Janssen COVID-19 vaccine may have reduced overall efficacy against disease caused by the Beta variant, compared to the other COVID-19 vaccines. Although sero-response rates were similar between U.S. clinical trial participants and those from Brazil and South Africa, vaccine efficacy against moderate to severe-critical COVID-19 after ≥14 days was 74% in the United States (where ~96% of infections were due to the ancestral strain with the D614G mutation), 66% in Brazil (where ~69% of infections were due to Zeta [P.2]), and 52% in South Africa (where ~95% of infections were due to Beta).(14) Notably, Janssen vaccine showed good efficacy against severe or critical disease (73%–82%) across all sites.

Box. Summary of vaccine efficacy estimates for approved or authorized COVID-19 vaccines

All approved or authorized COVID-19 vaccines demonstrated efficacy (range 65% to 95%) against symptomatic, laboratory-confirmed COVID-19 in adults ≥18 years.

- For each approved or authorized COVID-19 vaccine, efficacy was demonstrated across different populations, including elderly and younger adults, in people with and without underlying health conditions, and in people representing different races and ethnicities.
- The Pfizer-BioNTech COVID-19 vaccine also demonstrated high efficacy against symptomatic, laboratory-confirmed COVID-19 in adolescents aged 12-17 years.

All approved or authorized COVID-19 vaccines demonstrated high efficacy (≥89%) against COVID-19 severe enough to require hospitalization

require hospitalization.

All approved or authorized COVID-19 vaccines demonstrated high efficacy against COVID-19-associated death.

- In the clinical trials, no participants who received a COVID-19 vaccine died from COVID-19; the Moderna and Janssen vaccine trials among adults ≥18 years each had COVID-19 deaths in the unvaccinated placebo arm.

Data from the clinical trials among adults ≥18 years old suggest COVID-19 vaccination protects against symptomatic infection and may also protect against asymptomatic infection.

- In the Moderna trial, among people who had received a first dose, the number of asymptomatic people who tested positive for SARS-CoV-2 at their second-dose appointment was approximately 67% lower among vaccines than among placebo recipients (0.1% [n=15] and 0.3% [n=39], respectively)
- Efficacy of Janssen COVID-19 vaccine against asymptomatic infection was 74% in a subset of trial participants.

No trials have compared efficacy between any of the approved or authorized vaccines in the same study population at the same time, making comparisons of efficacy difficult.

- All Phase 3 trials differed by calendar time and geography.
- Vaccines were tested in settings with different background COVID-19 incidence and circulating variants.

Vaccine effectiveness from real-world studies

Multiple studies from the United States and other countries have demonstrated that a two-dose COVID-19 mRNA vaccination series is effective against SARS-CoV-2 infection (including both symptomatic and asymptomatic infections) caused by ancestral and variant strains and sequelae including severe disease, hospitalization, and death. Early evidence for the Janssen vaccine also demonstrates effectiveness against COVID-19 in real-world conditions. There is now a substantial volume of scientific literature examining the effectiveness of COVID-19 vaccination against SARS-CoV-2 infection, symptomatic disease, and other clinical outcomes; detailed summaries of these studies are available in the International Vaccine Access Center's VIEW-Hub resource library .

Several systematic reviews and meta-analyses of vaccine effectiveness have recently been published (15-17); meta-analyses indicate an average effectiveness of full vaccination against SARS-CoV-2 infection of 85%–95% shortly after completion of vaccination. (16, 17) However, many of the studies in these reviews were conducted prior to the emergence of the variants of concern. Studies in Israel, Europe, and the United Kingdom have demonstrated high real-world effectiveness (>85%) of two doses of Pfizer-BioNTech COVID-19 vaccine while the Alpha variant was prevalent.(18-26) Studies from Qatar have demonstrated high effectiveness against documented infection with Alpha and Beta ≥14 days after receiving the Pfizer-BioNTech vaccine (90% and 75%, respectively) and the Moderna vaccine (100% and 96%, respectively); importantly, both vaccines were 96%–100% effective against severe, critical, or fatal disease, regardless of strain.(27, 28) In three studies from Canada, one demonstrated 79% effectiveness for mRNA vaccines against confirmed infection during a time when Alpha and Gamma represented most infections, while another two demonstrated 84% and 88% effectiveness, respectively, against symptomatic infection caused by Gamma/Beta.(29-31)

Individual studies specifically examining vaccine effectiveness against the Delta variant or conducted in the context of substantial circulation of Delta are summarized in Table 1a and as follows. Studies from the United Kingdom have noted effectiveness of the Pfizer-BioNTech vaccine against confirmed infection (79%) and symptomatic infection (88%), compared with the Alpha variant (92% and 93%, respectively).(23, 25) A study from Canada demonstrated 87% effectiveness against symptomatic illness caused by the Delta variant ≥7 days after receipt of the second dose of Pfizer-BioNTech vaccine, compared with 89% for the Alpha variant.(32)Data from Qatar demonstrated 54% effectiveness against symptomatic illness for the Pfizer-BioNTech vaccine compared with 85% for the Moderna vaccine.(33). Preliminary data from South Africa on the effectiveness of the Janssen vaccine showed 71% effectiveness against hospitalization when Delta variant was predominant, compared to 67% when Beta was predominant. Data from Israel also suggest decreased effectiveness of vaccines against infection and illness caused by Delta. The variability in vaccine effectiveness estimates between countries may in part reflect differences in study methodology, intervals used between vaccine doses, and timing of vaccine effectiveness assessments. Of note, the United Kingdom and Canada used prolonged intervals of 12–16 weeks between vaccine doses, which have been observed to induce higher immunogenicity and effectiveness (including in ages ≥80 years) (34-37). The most recent estimates from Israel and Qatar represent time points >6 months after initiating respective national vaccination campaigns and 2–5 months after prior assessments of vaccine effectiveness against the Alpha variant, with

potential for waning immunity. Notably, in the United Kingdom, Canada, Qatar, South Africa, and Israel, vaccine effectiveness against hospitalization related to Delta was >90% and comparable to that observed with Alpha for all vaccines currently approved or authorized in the United States.(26, 32, 33)

Table 1a. *Effectiveness of COVID-19 Vaccination Against SARS-CoV-2 Infection and Symptomatic Disease (Including Severe Disease and Hospitalization) Caused by the Delta Variant*

Country	Population	Vaccine	Outcome	Vaccine Effectiveness*
UK[38]	General population ≥16 years	Pfizer-BioNTech	Symptomatic disease	88%[1](85-90)
Canada[32]	General population ≥16 years	Pfizer-BioNTech	Symptomatic disease	85%[1](59-94)
UK (Scotland)[25]	General population	Pfizer-BioNTech	SARS-CoV-2 infection	79%[1](75-82)
UK[23]	General population	Pfizer-BioNTech	SARS-CoV-2 infection	80%[1](77-83)
United States[39]	Healthcare workers, first responders, and other essential and frontline workers	Pfizer-BioNTech, Moderna, or Janssen	SARS-CoV-2 infection	66%[1](26-84)
United States[40]	Health system members ≥12 years	Pfizer-BioNTech	SARS-CoV-2 infection	75%[2](71-78)
			Hospitalization	93%[2](84-96)
Qatar[33]	General population ≥12 years	Moderna	SARS-CoV-2 infection	85%[1](76-91)
		Pfizer-BioNTech	SARS-CoV-2 infection	54%[1](44-61)
		Moderna	Symptomatic disease	86%[1](71-94)
		Pfizer-BioNTech	Symptomatic disease	56%[1](41-67)
		Moderna	Severe, critical, or fatal disease	100%[1](41-100)
		Pfizer-BioNTech	Severe, critical, or fatal disease	90%[1](61-98)
UK[26]	Patients hospitalized following ED visit	Pfizer-BioNTech	Hospitalization	96%[1](86-99)

*Only studies including estimates of vaccine effectiveness ≥7 days following a completed vaccination series of a COVID-19 vaccine currently approved or authorized for use in the United States are included here. For studies that examined variant-specific vaccine effectiveness against multiple variants of SARS-CoV-2, only estimates for effectiveness against the Delta variant are shown. The 95% confidence interval for each estimate of vaccine effectiveness is displayed in parentheses following the estimate.

[1]≥14 days after second dose

[2]≥7 days after second dose

In addition to preventing morbidity and mortality associated with COVID-19, currently approved or authorized vaccines also demonstrate effectiveness against asymptomatic SARS-CoV-2 infection. However, most studies of asymptomatic infection prevention were conducted in the context of circulation of different variants and the effectiveness of COVID-19 vaccines in preventing asymptomatic infection differs by variant and vaccine. In addition, infections identified in such studies as asymptomatic may simply have been identified prior to the infected person developing symptoms, i.e., these infections are presymptomatic rather than asymptomatic. Asymptomatic people are also less likely to be tested for SARS-CoV-2 infection in most settings and thus less likely to be captured in "real world" effectiveness studies.

Table 1b. *Effectiveness of COVID-19 Vaccination Against Asymptomatic SARS-CoV-2 Infection When Different Variants Predominated*

Country	Population	Vaccine	Dominant Variant(s)	Vaccine Effectiveness*
Israel [24]	Healthcare workers	Pfizer-BioNTech	Alpha	65%[1](45-79)
United States (California) [41]	General population ≥18 years	Pfizer-BioNTech or Moderna	Epsilon, Alpha	68%[2](29-86)
United States[42]	Preprocedural adult patients	Pfizer-BioNTech or Moderna	Ancestral strain	80%[3](56-91)
Qatar[33]	General population ≥12 years	Moderna	Delta	80%[4](54-93)
		Pfizer-BioNTech	Delta	36%[4](11-54)
Israel[43]	Healthcare workers	Pfizer-BioNTech	Alpha	86%[5](69-93)
Israel[21]	General population ≥16 years	Pfizer-BioNTech	Alpha	92%[5](91-92)
Israel[19]	General population ≥16 years	Pfizer-BioNTech	Ancestral strain, Alpha	90%[5](83-94)

*The 95% confidence interval for each estimate of vaccine effectiveness is displayed in parentheses following the estimate.

[1]≥11 days after second dose
[2]≥15 days after second dose
[3]≥0 days after second dose
[4]≥14 days after second dose
[5]≥7 days after second dose

Vaccine immunogenicity and effectiveness in immunocompromised people

Vaccination is particularly important for people with immunocompromising conditions, who are at increased risk of severe COVID-19 illness. However, current evidence suggests reduced protection from COVID-19 vaccines for many immunocompromised persons. Recent studies in several countries found significantly lower vaccine effectiveness among immunocompromised adults compared to those without immunocompromising conditions (44-46) (Table 2), although each study defined the immunocompromised population differently. Studies in the United States and Israel have also found that immunocompromised persons account for a high proportion (≥40%) of infections among fully vaccinated hospitalized persons. (46, 47)

Compared with those who are not immunocompromised, reduced antibody response to a two-dose primary series of mRNA COVID-19 vaccines has also been observed in specific groups of immunocompromised adults, including people receiving solid organ transplants (48-54); some people with cancer, particularly hematologic cancers (55, 56); some people receiving

hemodialysis for kidney disease (57, 58); and people taking certain immunosuppressive medications (51, 53, 54, 59). While antibody measurement and threshold levels varied by study, a large proportion of immunocompromised persons overall had a measurable immune response after a two-dose series of mRNA vaccine, although some remained seronegative. The distribution of antibody response by immunocompromising condition in several recent studies is summarized in Figure 1.

Emerging data suggest an additional COVID-19 vaccine dose in immunocompromised people, typically administered at least 28 days after completion of the primary series, increases antibody response: in small observational studies of solid organ transplant recipients (60-63) or hemodialysis patients (64-66), 33%-54% of persons who had no detectable antibody response to an initial two-dose mRNA vaccine series developed an antibody response to an additional dose of a COVID-19 vaccine. A recently published randomized controlled trial demonstrated substantial increases in serologic immune response to a third dose of Moderna's mRNA vaccine compared with placebo among solid organ transplant recipients who previously received a two-dose series of that vaccine.(67) While these studies evaluated serologic immune response to an additional vaccine dose, the clinical impact of an additional dose on acquisition, severity, and infectiousness of infections in fully vaccinated immunocompromised persons is not yet known.

Table 2. *Effectiveness of COVID-19 Primary Series Vaccination Against SARS-CoV-2 Infection and Symptomatic Disease among Immunocompromised Persons*

Country	Population	Vaccine	Outcome	Dominant Variant(s)	Vaccine Effectiveness in IC Population	Vaccine Effectiveness in Comparison Population*
United States[45]	Veterans ≥18 years taking immunosuppressive medications for inflammatory bowel disease	Pfizer-BioNTech or Moderna	SARS-CoV-2 infection	Unknown	69%[1](44-83)	No comparison
United States[68]	Solid organ transplant recipients	Pfizer-BioNTech, Moderna, or Janssen	SARS-CoV-2 infection	Ancestral strain, Alpha	81%[2](50-95)	No comparison
Israel[44]	General population ≥16 years	Pfizer-BioNTech	SARS-CoV-2 infection	Ancestral strain, Alpha	71%[1](37-87)	90%(79-95)
			Symptomatic disease		75%[1](44-88)	94%(88-97)
Qatar[69]	Kidney transplant recipients	Pfizer-BioNTech or Moderna	SARS CoV-2 infection	Alpha, Beta	47%[2](0-74)	No comparison
			Severe, critical, or fatal COVID-19 disease		72%[2](0-91)	
United States[46]	Hospitalized patients ≥18 years	Pfizer-BioNTech or Moderna	Hospitalization	Ancestral strain, Alpha	59%[2](12-81)	91%(86-95)

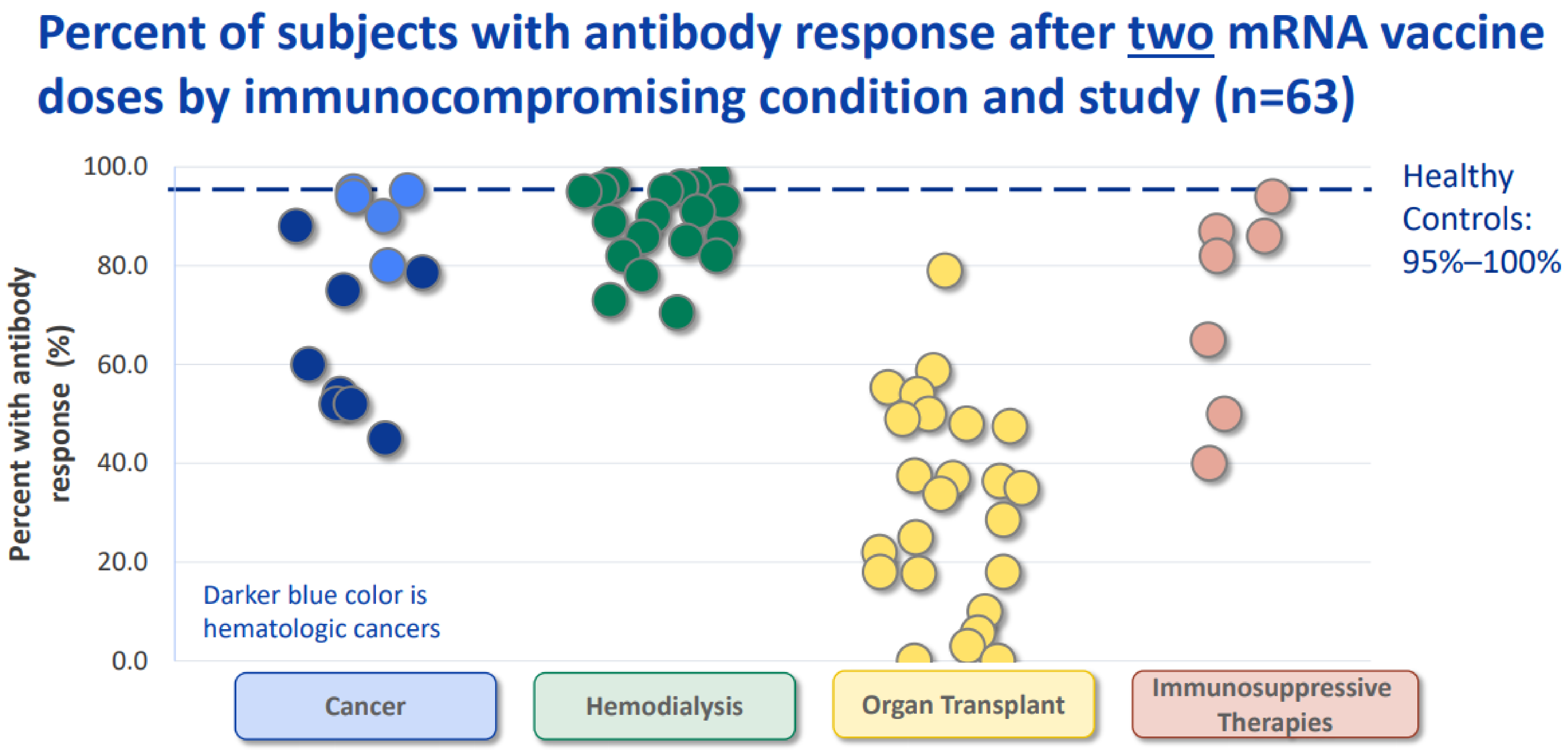
IC: Immunocompromised

* In the Israeli study, the comparison is with overall vaccine effectiveness (i.e., vaccine effectiveness in the entire study population, including those with immunocompromising conditions). In the U.S. study, the comparison is with vaccine effectiveness among members of the study population without immunocompromising conditions.

The 95% confidence interval for each estimate of vaccine effectiveness is displayed in parentheses following the estimate.

[1]≥7 days after second dose
[2]≥14 days after second dose

Figure 1:



*The studies displayed in Figure 1 represent the results of a literature review conducted by the Advisory Committee on Immunization Practices' COVID-19 Vaccines Work Group and are current as of July 21, 2021. Numerous additional studies of antibody response to COVID-19 vaccination in various immunocompromised populations have been published since that date and are not captured here.

Vaccine immunogenicity and effectiveness of heterologous (mixed) dosing regimens

Multiple small studies from Europe have examined the immunogenicity of a heterologous or 'mixed' series of COVID-19 vaccines. These studies found that receipt of a dose of AstraZeneca's adenovirus vector vaccine followed by a dose of an mRNA vaccine (most frequently Pfizer-BioNTech) induced a robust immune response (70-72) and was at least as immunogenic as two doses of mRNA vaccines by most measures of immune response.(73-79) One study examined vaccine effectiveness of this heterologous series and estimated an effectiveness of 88% against any SARS-CoV-2 infection two weeks following the mRNA (second) dose.(80) Only one study examined a heterologous series in which the mRNA vaccine was the priming (first) dose; this study found that a dose of Pfizer-BioNTech vaccine followed by a dose of AstraZeneca vaccine did not achieve non-inferiority of immune response when compared with two doses of Pfizer-BioNTech.(81) A single study to date examined heterologous dosing with a primary mRNA vaccine series followed by a dose of the Janssen adenovirus vector COVID-19 vaccine in four subjects and noted substantially increased immune response against SARS-CoV-2 after the third dose.(82)

Vaccine-induced neutralizing antibody activity

Sera from mRNA COVID-19 vaccine (both Pfizer-BioNTech and Moderna) recipients have demonstrated minimal to large reductions in antibody neutralization activity against a variety of mutations, as reviewed in VIEW-Hub. Two related systematic reviews and meta-analyses have also been published (83, 84); however, these reviews do not include all available neutralization studies of the Delta variant with sera from people who received mRNA vaccines or the Janssen vaccine.(85-96) Across studies of VOCs, the greatest reductions were observed for Beta, followed by Gamma and Delta; reductions for Alpha were minimal. The E484K/Q and L452R mutations alone or in combination with other mutations in the receptor binding domain have been shown to account for the majority of the reduction in vaccine-induced neutralizing antibody activity for the Beta, Gamma, and Delta variants.(97-103) Alpha and Iota variants with E484K mutations, which have been detected in the United Kingdom, United States, and other countries, have shown further reductions in neutralization above Alpha and Iota alone, respectively.(87, 97, 104-109) For two-dose COVID-19 vaccines, multiple studies have shown greater neutralization against variants after the second dose (i.e. among fully vaccinated people) compared with after the first dose alone.(88, 91, 97, 98, 110-118)

98, 110-118)

Robust correlation has been demonstrated between vaccine efficacy and neutralizing antibody levels induced by different vaccines.(119, 120) Based on evidence from clinical trials, the correlate of protection, or antibody threshold providing protection against severe disease, has been estimated to be much lower than that required for protection against confirmed infection.(120) However, in the absence of an accepted antibody threshold that correlates with protection, it is difficult to fully predict how reduced neutralizing activity may affect COVID-19 vaccine effectiveness. Some variants may reduce neutralizing antibody levels to near or below the protective threshold, resulting in lowered vaccine efficacy, increased infections in vaccinated persons, and shortened duration of immunity, and others may not be significant.

Vaccine-induced cellular immunity

Several studies have assessed CD4+ and CD8+ T cell responses from Moderna or Pfizer-BioNTech vaccine recipients to the ancestral SARS-CoV-2 strain compared with the Alpha, Beta, Gamma, and Epsilon variants; these studies observed modest or no defects in cellular immune recognition of the variants.(112, 116, 121-126) Thus, cellular immunity may help limit disease severity in infections caused by variants that partially escape neutralizing antibodies. Variations in the genes encoding human leukocyte antigens have been observed to result in variation of the T cell response to specific SARS-CoV-2 variants, which may impact different subpopulations differently based on genetic prevalence of these variations.(127-132) There are currently no studies of vaccine-induced cellular immunity against the Delta variant.

Older adults and long-term care facility residents

Multiple studies have noted reduced vaccine effectiveness in older adults (≥60 years) (38, 133-135) or residents of long-term care facilities, compared with general population estimates.(136-138) Compared with younger individuals, persons aged >80 years have been noted to have reduced T-cell responses, lower neutralizing antibody levels, and less potential antibody diversity (somatic hypermutation), potentially giving this group increased risk for susceptibility to SARS-CoV-2 infection in vaccinated people. (139) Two studies have observed poor antibody response to the Pfizer-BioNTech vaccine among nursing home residents compared with staff (140, 141); one study noted 38% of nursing home residents had undetectable antibodies to the Beta variant at 2–4 weeks after the second dose of Pfizer-BioNTech vaccine, compared with 12% with Moderna vaccine. (140) Another study showed declining antibody levels among nursing home residents, with 72% of residents having undetectable neutralizing antibody levels at 6 months post-vaccination with Pfizer-BioNTech.(142)

Duration of protection

Immunogenicity of COVID-19 vaccines has been demonstrated out to 6–8 months after vaccination.(86, 143) At 2–3 months post vaccination, two studies have shown lower neutralizing titers, including against the Beta and Delta variants, for Janssen (an adenovirus vector vaccine) compared with the mRNA vaccines.(144, 145) Two studies have shown a combined impact of waning antibody levels and reduced neutralization of variants; six months after receiving the Moderna vaccine, neutralizing antibody levels were reduced but sufficient to protect against the ancestral strain, while about 50% of people had undetectable neutralization activity against Beta and Gamma compared with the ancestral strain.(146, 147) However, a small study of people 8 months after receiving the Janssen vaccine had minimal decline in neutralizing titers against Beta, Gamma, and Delta and there was evidence of expanded breadth of neutralizing antibody response against variants over this time period, likely through B cell maturation.(86) More evidence is still needed in this area, including understanding potential differences in the kinetics of immune response related to different vaccine platforms. One recent modeling study based on immunogenicity data predicted that vaccine effectiveness against symptomatic infection caused by the Delta variant may drop below 50% within the first year after vaccination for most current vaccines in use globally, while the majority are protected from severe illness.(148)

Six-month clinical efficacy for the Pfizer-BioNTech vaccine shows an overall efficacy against infection of 91% and 97% efficacy against severe illness.(149) However, a non-significant decrease of six percentage points was observed for every two months ≥7 days post-vaccination, from 96% at ≥7 days to <2 months, 90% at 2 to <4 months, and 84% at 4 to <6 months. Similar results for the Moderna vaccine have not yet been published, but data from the manufacturer cite 93% overall efficacy up to 6 months.

Several recent studies have noted decreases over time in the effectiveness of COVID-19 vaccines against SARS-CoV-2 infection. A study of U.S. long-term care residents, who were among the first groups in the United States to be vaccinated, found effectiveness of mRNA vaccination against infection declined from 75% in March–May 2021 to 53% in June–July 2021. (150) A study of adults in one U.S. state found a decline in vaccine effectiveness against SARS-CoV-2 infection from 92% the week of May 3, 2021 to 80% the week of July 19, 2021.(151) Two studies in large U.S. health systems examined mRNA vaccine effectiveness longitudinally from December 2020 and January 2021 through July 2021 and August 2021 and noted marked declines over this period (40, 152); similarly, a large population-based study in the UK identified decreases in effectiveness of

Pfizer-BioNTech vaccination over 4-5 months following the second dose.(153) Observed changes in vaccine effectiveness against infection with SARS-CoV-2 may reflect reduced vaccine performance against the Delta variant, waning immunity from primary vaccination, or other unmeasured confounders. In addition, as people at the highest risk of SARS-CoV-2 infection were generally vaccinated first, observational studies of duration of immunity may be subject to confounding by risk status. Importantly, data as of July 2021 confirm sustained high effectiveness of full mRNA vaccination against COVID-19 hospitalization, even up to 6 months post-vaccination.(151, 154)

A retrospective cohort study in a large healthcare system in Israel noted a 2.3-fold increased risk for infection among fully vaccinated persons who were vaccinated with Pfizer-BioNTech in January vs. April 2021.(155) A similar study observed a higher rate (2.4% v. 1.1%, OR=2.2) of infection in fully vaccinated persons who received the second Pfizer-BioNTech dose ≥5 months ago compared with those who received it <5 months ago, with higher magnitude of difference with increasing age.(156)

Infections in fully vaccinated persons: clinical implications and transmission

As expected, because no vaccines is 100% effective, infections in fully vaccinated persons (e.g. breakthrough infections) have been observed, albeit at much lower rates than infections among unvaccinated persons; vaccine effectiveness against severe disease remains high. From January through June 2021, COVID-NET data from laboratory-confirmed COVID-19-associated hospitalizations in adults ≥18 years of age for whom vaccination status is known showed 3% of hospitalizations occurred in fully vaccinated persons. In general, symptoms and duration of illness in infections among fully vaccinated persons have been attenuated compared with cases among unvaccinated people.(157) CDC conducts nationwide monitoring of infections in fully vaccinated persons resulting in hospitalization or death. Among hospitalized or fatal cases reported to CDC as of August 30, 2021, 70% of hospitalized cases and 87% of fatal cases of COVID-19 in fully vaccinated persons were in persons aged 65 years or older. Infections in fully vaccinated persons may be associated with lower antibody levels compared with those who maintain protection, as shown in a study of fully vaccinated healthcare workers in Israel with infections caused by the Delta variant.(158) However, infection in a fully vaccinated person may boost immunity; four weeks after an outbreak in a long-term care facility, fully vaccinated residents who experienced SARS-CoV-2 infections were found to have significantly higher antibody levels than vaccinated individuals who did not experience SARS-CoV-2 infections.(159)

The proportions of VOCs observed among cases in fully vaccinated persons has been similar to that observed in CDC's national genomic surveillance,(160) but interpretation of these data are challenging because of local variation and changes in variant proportions over time. An Israeli study of VOC infections in adults fully vaccinated with Pfizer-BioNTech vaccine compared with unvaccinated matched controls, during a time when Alpha was the dominant strain and Beta was detected in <1% of all specimens, found a higher proportion of Beta in fully vaccinated cases (matched odds ratio = 8.0) and a higher proportion of Alpha in partially vaccinated cases (matched odds ratio = 2.6), though small sample sizes, especially for Beta, were noted as a limitation.(161) Results of a study from Maryland showed that variants with E484K substitutions (e.g., Beta, Gamma) were associated with increased odds of SARS-CoV-2 infection (OR=2.0) in fully vaccinated persons and infection in fully vaccinated persons associated with hospitalization (OR=2.6), while L452R substitutions (e.g., Delta) were not.(162) However, a study from Houston, Texas observed that Delta caused a significantly higher rate of infections in fully vaccinated people compared with infections from other variants, but noted that only 6.5% of all COVID-19 cases occurred in fully vaccinated individuals(163); similar findings were noted in India.(96)

In studies conducted before the emergence of the Delta variant, data from multiple studies in different countries suggested that people vaccinated with mRNA COVID-19 vaccines who develop COVID-19 generally have a lower viral load than unvaccinated people.(157, 165-169) This observation may indicate reduced transmissibility, as viral load has been identified as a key driver of transmission.(170) Studies from multiple countries found significantly reduced likelihood of transmission to household contacts from people infected with SARS-CoV-2 who were previously vaccinated for COVID-19.(171-176) For the Delta variant, early data indicate vaccinated and unvaccinated persons infected with Delta have similar levels of viral RNA and culturable virus detected, indicating that some vaccinated people infected with the Delta variant of SARS-CoV-2 may be able to transmit the virus to others.(163, 164, 177-180) However, other studies have shown a more rapid decline in viral RNA and culturable virus in fully vaccinated people (96, 177, 180-182). One study observed that Delta infection in fully vaccinated persons was associated with significantly less transmission to contacts than persons who were unvaccinated or partially vaccinated.(181)

Together, these studies suggest that vaccinated people who become infected with Delta have potential to be less infectious than infected unvaccinated people. However, more data are needed to understand how viral shedding and transmission from fully vaccinated persons are affected by SARS-CoV-2 variants, time since vaccination, and other factors, particularly as

transmission dynamics may vary based on the extent of exposure to the infected vaccinated person and the setting in which the exposure occurs. Additional data collection and studies are underway to understand the extent and duration of transmissibility of Delta variant SARS-CoV-2 in the United States and other countries.

Conclusions

COVID-19 vaccines currently approved or authorized in the United States have been shown to provide considerable protection against severe disease and death caused by COVID-19. These findings, along with the early evidence for reduced levels of viral mRNA and culturable virus in vaccinated people who acquire SARS-CoV-2 infection, suggest that any associated transmission risk is substantially reduced in vaccinated people: even for Delta, evidence suggests fully vaccinated people who become infected are infectious for shorter periods of time than unvaccinated people infected with Delta. While vaccine effectiveness against emerging and other SARS-CoV-2 variants will continue to be assessed, available evidence suggests that the COVID-19 vaccines approved or authorized in the United States offer substantial protection against hospitalization and death from emerging variants, including the Delta variant. Data suggest lower vaccine effectiveness against laboratory-confirmed illness and symptomatic disease caused by the Beta, Gamma, and Delta variants compared with the ancestral strain and Alpha variant. Early data also find some decline in vaccine effectiveness against SARS-CoV-2 infection over time, although in fall 2021, 9 months after the start of the U.S. COVID-19 vaccination program, vaccination remains highly protective against hospitalization with COVID-19.

Evidence suggests the U.S. COVID-19 vaccination program has substantially reduced the burden of disease in the United States by preventing serious illness in fully vaccinated people and interrupting chains of transmission. Vaccinated people can still become infected and have the potential to spread the virus to others, although at much lower rates than unvaccinated people. The risks of SARS-CoV-2 infection in fully vaccinated people are higher where community transmission of the virus is widespread. Current efforts to maximize the proportion of the U.S. population that is fully vaccinated against COVID-19 remain critical to ending the COVID-19 pandemic.

*Note: This brief summarizes evidence related to vaccines approved or authorized for emergency use in the United States. In specific circumstances, CDC guidance for fully vaccinated people can also be applied to COVID-19 vaccines that have been listed for emergency use by the World Health Organization (e.g. AstraZeneca/Oxford) and to some vaccines used for U.S. participants in COVID-19 vaccine trials.

Previous Updates

Updates from Previous Content

As of July 27, 2021

- Data were added from studies published since the last update that demonstrate currently authorized mRNA vaccines provide protection against variants of concern, including the Delta strain that is now predominant in the United States. Vaccine effectiveness against hospitalization and death is high for all current SARS-CoV-2 variants; emerging data suggest lower effectiveness against confirmed infection and symptomatic disease caused by the Beta, Gamma, and Delta variants compared with the ancestral strain and the Alpha variant.

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Note: Preprints have not been peer-reviewed. They should not be regarded as conclusive, guide clinical practice/health-related behavior, or be reported in news media as established information.

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Previous Updates

As of May 27, 2021

- Data were added from studies published since the last update that further demonstrate currently authorized COVID-19 vaccines are effective against SARS-CoV-2 infection, symptomatic and severe disease, and hospitalization with COVID-19.
- Data were added suggesting that currently authorized mRNA vaccines provide protection against variants of concern, including the B.1.1.7 strain that is predominant in the United States.
- Data were added from studies published since the last update that further demonstrate people who are fully vaccinated with a currently authorized mRNA vaccine are protected against asymptomatic infection and, if infected, have a lower viral load than unvaccinated people.

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